REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 12-14, 16, 18-23, 25, 27-30 and 37-40 are pending after entry of the amendments set forth herein.

Claims 12, 13, 18-21, 25 and 27-36 were examined and rejected.

Claims 12, 13, 19, 21 and 25 are amended and claims 37-40 are new. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for embryonic stem cells, cultured gastrointestinal organ cells (including, specifically, liver and pancreas cells) is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: paragraph 175 on page 46 and paragraph 130 on page 32. Accordingly, no new matter is added by these amendments.

Claims 15 and 31-36 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Drawings

Corrected drawing sheets for Figs. 18 and 19 are filed herewith.

Acceptance of these drawing sheets is respectfully requested.

Withdrawn claims

Applicants note that claims 14, 16, 22 and 23 are withdrawn because they are directed to neuroendocrine transcription factors other than ngn3, the species of neuroendocrine transcription factor elected for initial examination.

These withdrawn claims are dependent on generic claims 12 and 19. Pursuant to the instructions set forth in MPEP §809.02(c), claims 14, 16, 22 and 23 should be rejoined with claims 12 and 19 upon

allowance of claim 12 and 19.

Accordingly, the Applicants respectfully request rejoinder of claim 14, 16, 22 and 23 if claims 12 and 19 become allowable.

Interview summary

The Applicants wish to express their gratitude to Examiner Whiteman and Supervisory Examiner Reynolds for the interview on October 21, 2003, with Applicants' representatives James Keddie, Carol Francis and Michael German.

Two aspects of an outstanding rejection under 35 U.S.C. §112, first paragraph (enablement) were discussed during the interview, as well as arguments to overcome the rejections.

The first aspect of the rejection, as detailed in the Office Action, relates to the scope of neuroendocrine bHLH transcription factors that could be used in the subject methods. Dr. German presented scientific reasoning why any neuroendocrine bHLH transcription factor could be used in the claimed methods. The Examiners indicated that the reasoning was convincing.

The second aspect of the rejection, as detailed in the Office Action, relates to the scope of cells that could be used in the subject methods. Dr. German presented scientific reasoning why any mammalian cell could be used in the claimed methods. An agreement was not reached, although the Examiners did indicate that embryonic stem cells and cells of the gut (e.g., liver and pancreatic cells) could be used in the subject methods.

Claim objections

Claims 12 and 19 are objected to because of the spelling of the word "neuroendocrine".

Claims 12 and 19 have been amended to recite the word "neuroendocrine", and, as such, this objection may be withdrawn.

Claims 32, 33, 35 and 36 are objected to for reading on a non-elected species.

Claims 32, 33, 35 and 36 have been cancelled, and, as such, this objection is moot and may be withdrawn.

Claim 31 is objected to for being a duplicate of claim 12.

Claim 31 has been cancelled, and, as such, this objection is moot and may be withdrawn.

Claim 34 is objected to for being a duplicate of claim 19.

Claim 34 has been cancelled, and, as such, this objection is moot and may be withdrawn.

Rejection under 35 U.S.C. §112, first paragraph (enablement)

Claims 12, 13, 18-21, 25 and 27-30 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was assertedly not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Applicants respectfully traverse this rejection.

Since there are two aspects to this rejection, the rejection will be addressed in two parts.

Neuroendocrine bHLH transcription factors

The Office argues that the art in the area of the claimed invention -- using neuroendocrine bHLH transcription factors to induce insulin-production in mammalian cells -- is unpredictable, and, accordingly, that the use of the claim-recited genus of neuroendocrine bHLH transcription factors to induce insulin-production in mammalian cells would require undue experimentation.

The Applicants have previously shown, by means of a declaration by Dr. Michael German, that three of the 10 known human neuroendocrine transcription factors shown in Fig. 10 of the instant application (namely neurogenin3, neuroD1 and mash1), have been successfully used to make insulin-producing cells. The Applicants argued, and Dr. German declared, that these examples are representative of the genus of neuroendocrine bHLH transcription factors recited in the claimed methods.

The Applicant's assertions are supported by the phylogenetic classification of human neuroendocrine bHLH transcription factors into three related, but separate, subgroups. The three neuroendocrine bHLH transcription factors of the working examples are each classified in a different phylogenetic subgroup. The working examples provide evidence that a neuroendocrine bHLH transcription factor from any of the three different phylogenetic subgroups, when expressed in a mammalian cell, provides for production of an insulin-producing cell.

A phylogenetic tree showing the phylogenetic relationship between all of the human neuroendocrine bHLH transcription factors, including the working examples, is shown in Exhibit A, attached herewith. Neurogenin3, successfully used in the subject methods, is a member of the first subgroup (the neurogenins: ngn3, ngn1 and ngn2), neuroD1 is a member of the second subgroup (the

neuroDs: neuroD1, neuroD2, neuroD3 and math2), and mash1 is a member of the third subgroup (the mash factors: mash1 and mas2). Since the Applicants have provided a working example for each subgroup of neuroendocrine bHLH proteins, the Applicants respectfully submit that one of skill in the art would recognize that the genus of neuroendocrine bHLH islet transcription factors could be used in the claimed methods without undue experimentation.

In response to the Applicant's assertions, the Office asserted in the present Office Action that Anderson (USPN 6,566,496) demonstrates that certain neuroendocrine class B bHLH proteins (e.g., ngn1 and ngn2) are not detectably expressed in islet cells and therefore cannot be used in the subject methods.

As discussed during the interview, all of the known human neuroendocrine bHLH proteins (i.e. those shown in Fig. 10 and Exhibit A) are either expressed in mature islet cells or during specific periods islet cell development. Anderson's observations are likely due to the fact that ngn1 and ngn2, like many other neuroendocrine class B bHLH proteins, are only expressed at a specific period of islet cell development and are not expressed in other periods (or are expressed at very low levels that would be difficult to detect using the method set used by Anderson). Accordingly, the Applicants respectfully submit that ngn1 and ngn2 are not expressed in the particular islet cell precursors examined by Anderson. They are, however, expressed in other islet cell precursors.

Further, the Applicants also note that Anderson uses *in situ* hybridization to detect gene expression. *In situ* hybridization is not a sensitive method for detecting gene expression, and, since many neuroendocrine bHLH proteins are expressed in islet cell precursors in relatively low amounts, Anderson may not been able to detect ngn1 or ngn2, even if they were expressed in the particular islet cell precursors at the particular timepoint examined by Anderson.

Accordingly, the Applicants respectfully submit that the Anderson's showing that certain islet cell precursors do not express certain neuroendocrine bHLH proteins is actually consistent with their use in the subject methods.

The Office also argues that the art of record indicates that HIF-1 cannot be used in the subject methods.

The Applicants respectfully submit that HIF-1 is a "PAS" bHLH and not a neuroendocrine bHLH. This assertion is evidenced in Exhibit B, in which HI-1 is referred to as a "helix-loop-helix

protein of the PAS family". HIF-1 is not a neuroendocrine h-bHLH transcription factor and a method that uses HIF-1 to make insulin-producing cells is not encompassed the rejected claims. The question of whether HIF-1 may be used to make insulin-producing cells, therefore, has no bearing on the patentability of the rejected claims.

Cell types

The Office argues that the claimed method encompass the use of an unreasonably large number of cell types, and, as such, the claims fail to meet the enablement requirement of 35 U.S.C. §112.

As discussed during the interview, there are a number of reasons why one of skill in the art would expect a wide variety of cell types to work. Accordingly, the Applicants disagree with this rejection.

However, solely to expedite prosecution and without wishing to acquiesce to the correctness of this rejection, the claims are amended to recite "an embryonic stem cell or a cultured gastrointestinal organ cell".

The Applicants respectfully submit that, in view of the Applicant's actual reduction to practice of the claimed methods using liver and pancreas cells, a skilled person would recognize that the claimed methods could be used with a wide variety of cells, including, embryonic stem cells and cultured gastrointestinal organ cells, e.g., cultured liver and pancreas cells. The Applicants note that cultured liver and pancreas cells are specifically recited in claims 37-40. Claim 25 recites a "pancreatic cell".

In view of the foregoing discussion, withdrawal of both aspects of this rejection is respectfully requested.

Claim rejection under 35 U.S.C. § 112, second paragraph

Claims 12, 13, 21, 25, 30, 31 and 34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

Claims 12, 13 and 21 are rejected for reciting "the islet transcription factor".

These claims have been amended to recite "the *neuroendocrine bHLH* transcription factor.

The Applicants respectfully submit that the meaning of the claim is now clear and that this rejection may be withdrawn.

Claims 25 and 30 are rejected for reciting "a nucleic acid molecule operably linked to a promoter, a nucleic acid molecule encoding neurogenin2 (Ngn3)", which is assertedly unclear.

Claim 25 has been amended to recite "a nucleic acid molecule operably linked to a promoter, *the* nucleic acid molecule encoding neurogenin3 (Ngn3)".

The Applicants respectfully submit that the meaning of the claim is now clear and that this rejection may be withdrawn

Claims 31 and 34 are also rejected as being indefinite. However, these claims are now cancelled, and, accordingly, this rejection may be withdrawn.

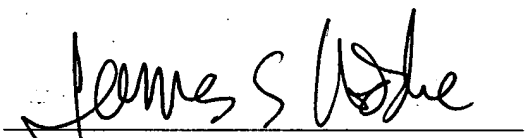
CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCSF-129CIP.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: December 4, 2003

By: 
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Enclosures: Exhibit A – phyogenetic tree
Formal Figures 18 and 19